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(21) International Application Number: PCT/EP91/00688 (22) International Filing Date: 9 April 1991 (09.04.91) (30) Priority data: 20054 A/90 17 April 1990 (17.04.90) IT (71) Applicant: EURAND INTERNATIONAL SPA [IT/IT]; Via M. De Vizzi, 60, I-20092 Cinisello B (IT). (72) Inventors: CALANCHI, Massimo, Maria ; Via Calatafini, 12, I-20052 Monza (IT). ZEMA, Marco ; Via G. Verga, 10, I-22100 Como (IT). GIORGETTI, Enzo ; Viale Pal- monova, 191, I-20132 Milan (IT). BRUNETTI, Gabriele ; Viale dei Mille, 27, I-20129 Milan (IT).		(74) Agents: WILEMAN, D., F. et al.; Wyeth Laboratories, Huntercombe Lane South, Taplow Nr. Maidenhead, Berkshire SL6 0PH (GB). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CH (European patent), DE (European pa- tent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (Euro- pean patent), IT (European patent), JP, KR, LU (Euro- pean patent), NL (European patent), SE (European pa- tent), SU. Published <i>With international search report.</i>
(54) Title: CONTROLLED RELEASE DRUG FORMULATION (57) Abstract The invention provides a targeted drug release formulation for delivery of drugs to the small intestine and colon of a mam- mal consisting essentially of a plurality of multidose units each said unit having a particle size of less than about 5mm and con- sisting essentially of a core of a drug (free of aminosalicic acid functional groups and excluding anti-inflammatory and antiph- logistic drugs having a local action in the intestine, corticosteroids for the local treatment of chronic intestinal inflammation or irritation, and peppermint oil) surrounded by two membranes, one membrane consisting essentially of a pH dependent polymer which is substantially soluble at a pH greater than about 5.0, and the second of said membranes consisting essentially of one or more polymers such that said second membrane is substantially insoluble in but permeable to gastro-intestinal fluids. Said formu- lation is characterized by the release of no more than about 10 % drug into the stomach with all of the remainder of the drug be- ing released in the small intestine and/or colon in a period from about 1/2 hour to about 8 hours.		

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CONTROLLED RELEASE DRUG FORMULATION

The present invention relates to a controlled release drug formulation and method for obtaining a targeted and controlled release of drugs which must carry out their pharmacological action in the intestine and in particular in the small intestine and/or colon.

USA patent 4,503,030 refers to tablets with osmotic release, consisting of a core containing the drug, covered with a semipermeable and pH-dependent membrane in which a hole is made to put the nucleus in communication with the outside. In the stomach, the tablet remains intact and the release occurs through the hole made in the membrane, while in the intestine the membrane disintegrates completely.

USA patent 4,432,966 describes the preparation of tablets which disintegrate in the colon. This is achieved by coating the tablet core with two layers.

The first is made up of a pH independent polymer and microcrystalline cellulose, the second of a pH dependent polymer. The presence of microcrystalline cellulose together with the pH independent polymer, is essential to assure the disgregation of the tablet in the colon, since the microcrystalline cellulose is digested by specific enzymes and the bacteria present in the colon.

The present invention has various advantages with respect to those cited above as it relates to multidose forms instead of monodose forms.

It is known that multidose forms spread in a wide area of the gastro-intestinal tract avoiding and reducing problems of irritation of the mucosa due to a high

concentration of the drug, and improving absorption of the same drug.

Moreover in the present invention while the pH dependent membrane dissolves when the coated particles reach the proper pH in the intestine, the pH independent membrane remains intact in order to delay the dissolution of the drug, in a time which can vary from about 30 minutes to about 8 hours, and consequently prolong its action along the small intestine and/or the colon.

10 According to the present invention there is provided a targeted drug release formulation for delivery of drugs to the small intestine and colon of a mammal consisting essentially of a plurality of multidose units each said unit having a particle size of less than about 5mm and
15 consisting essentially of a core of a drug (free of aminosalicyclic acid functional groups and excluding anti-inflammatory and antiphlogistic drugs having a local action in the intestine, corticosteroids for the local treatment of chronic intestinal inflammation or irritation, and peppermint oil) surrounded by two
20 membranes, one membrane consisting essentially of a pH dependent polymer which is substantially soluble at a pH greater than about 5.0, and the second of said membranes consisting essentially of one or more
25 polymers such that said second membrane is substantially insoluble in but permeable to gastrointestinal fluids. Said formulation may be further characterised by the release of no more than about 10% of drug in the stomach (or at a pH lower than
30 about 4.5) with a dissolution rate such that over a period of about 30 minutes to about 8 hours substantially all of the remaining drug is released in the intestine and/or colon (or at a pH of 5 or more in simulated gastrointestinal medium). The release may be
35 further characterised by the release of no more than

about 11% drug after 3 hours and no more than about 75% drug after 6 hours in simulated gastric fluid. Another embodiment is where the dissolution is to occur in the small intestine it is preferred that substantially all of the release (90%) occurs between 1 hour and 1½ hours at pH 6.8, with no more than 10% release occurring in the stomach.

Typical pH values are 1 to 3.5 for the stomach, 5 to 6, for the duodenum, 6 to 7 for the jejunum and pH 7 to 8 for the ileum.

The present invention is suitable not only for drugs which act in the intestine, in particular in the colon, but also for drugs which are destroyed by gastric juices or inactivated by enzymes such as for example pancreatic and bacterial proteases of the ileum. Cited as an illustrative, but not limiting, examples of these drugs are: penicillin G, calcitonin, heparin, ferritin, sucralfate, mebeverine hydrochloride, acarbose, dimethicone and simethicone, immunoglobulin, anthelmintics, anti-protozoa, local and general action intestinal anti-infectants and antifungal drugs. From the present invention the following are disclaimed: drugs having aminosalicyclic acid functional groups, anti-inflammatory and antiphlogistic drugs having a local action in the intestine, corticosteroids for local treatment of chronic intestinal inflammation or irritation and peppermint oil.

For some diseases of the intestine, and in particular of the colon, it is important that the drugs are transported intact to the place in which they will carry out their pharmacological action.

This is achieved by coating them with a membrane with pH-dependent solubility, and more particularly with a membrane which is soluble at a pH greater than 5.0, so that it remains intact in the stomach and first part of the intestine while it dissolves when a pH of greater than 5.0 is reached in the intestine, thus releasing the drug. But for various drugs it is also important that the contact with the mucosa, or their absorption, occurs along all the colon, and therefore it is necessary to delay the release so that the effect is prolonged in time and does not occur only in the initial tract, as happens when the drug is covered with the pH dependent membrane only.

It has now been discovered that by applying separately a membrane with pH dependent solubility and a membrane which is insoluble but permeable to gastrointestinal fluids, the dissolution of the drug can be delayed; it is released slowly and can thus carry out its action along the small intestine or the colon, or both. In fact (see Example 1) if the drug is coated by a Eudragit S membrane, (which dissolves at a pH higher than 7) there is a very low release in buffered solutions up to pH 6.2 (first 3 hours), but when the pH increases to 7.2 a rapid dissolution of the drug occurs.

Only by applying a second membrane of ethylcellulose, which is insoluble in the juices but permeable to same, on to the Eudragit membrane, is one able to delay the release of the drug and to prolong the effect for another 3 hours.

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The same result is obtained if the delaying membrane (see Example 2) is applied before the pH dependent membrane, while if the two types of polymers constituting the membrane (Example 3) are mixed, the delayed effect is not obtained. Instead there is a release very similar to that obtained by applying only the pH dependent polymer.

Moreover, the drug can be targeted to the small intestine or to the colon by making a suitable choice of the pH dependent polymer. For example if we use as pH dependent membrane Eudragit L30D, that is soluble at pH higher than 5.5, it is dissolved in the duodenum, then the pH independent membrane delays the release of the drug along the jejunum or the jejunum plus ileum or the small intestine plus colon depending from the permeability and the amount of pH independent membrane applied on the core. On the contrary, if we use as pH dependent membrane Eudragit S, that is soluble at pH higher than 7, it is dissolved only in the ileum, therefore the pH independent membrane will prolong the release of the drug only along the colon.

The original characteristic of the present invention consists therefore of the consecutive application, in any order, of a membrane soluble at a given pH and an insoluble but permeable membrane.

Thus a release of the drug targeted at a certain tract of the intestine and a prolonging of this release is obtained in such a way as to render it effective along the whole of the remaining intestinal tract.

Description of the Process for Coating with the First Membrane

5 The present invention is applied to multidose forms, that is drugs in the form of crystals, granules, pellets or tablets of very small dimensions, (also called minitabets) which are coated as described later. These coated drugs are then formulated in capsules, monodose sachets, in rapidly disgregating tablets or in other pharmaceutical forms suitable for oral administration.

10 The sizes of the single units of the multidose forms, that is of the single crystals, granules, pellets or minitabets, may vary from 0.1 to 3.5 mm but must not exceed 5 mm.

15 In fact the smaller the single units are, the wider the distribution in the gastrointestinal tract, and furthermore, while the units greater than 5 mm are retained in a full stomach, units smaller than 5 mm pass through the stomach much more rapidly and in a similar way to liquids.

20 This phenomenon is described in the article by S.S. Davis "The Design and Evaluation of the Controlled Release Systems for the Gastrointestinal Tract" published in the "Journal of Controlled Release", 2(1985)27-38.

25 Since the drugs are often in fine powder form, these are generally granulated, using known dry or wet techniques (compacting), to obtain the desired particle size.

However it should be considered that the description which follows, that is referring to drugs in granular form is also valid for the other multidose forms, i.e., crystals, pellets and minitables.

- 5 The granulated drug is placed in a UNI Glatt fluid bed container equipped with the Wurster insert and is coated, by spraying through atomiser, with a pH dependent polymer, dissolved in an organic solvent, or
10 in a mixture of organic solvents, or in a mixture of organic solvents and water, or in solution, dispersion or aqueous emulsion.

- It is also convenient to add plasticisers. Among the types of polymers constituting the pH dependent membrane the following are cited as an illustrative but
15 not limiting example: anionic co-polymers of methacrylic acid and methacrylic acid methyl or ethyl ester (e.g. Eudragit L, S, L30D, L100-55), cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, (e.g. HP 50) polyvinyl acetate phthalate,
20 shellac, hydroxypropylmethyl-cellulose acetate succinate, (e.g. AS-L) carboxymethylcellulose, cellulose acetate trimellitate, copolymers of maleic acid and phthalic acid derivatives.

- Cited among the plasticisers are polyethylene glycol, dibutyl phthalate, diethyl phthalate, citric acid
25 esters and among the adjuvants: talc, silicon dioxide, titanium dioxide, magnesium stearate, again as an illustrative but not limiting example.

- The coated granules are dried, e.g. with hot air (about
30 50 degrees C) for about 30 minutes.

Description of the Second Membrane Coating Process

These granules coated with pH dependent membrane are then coated with a second pH independent membrane using analogous techniques. Also in the case one can use organic or aqueous solutions or aqueous dispersions/
5 emulsions and it is convenient to add plasticisers and adjuvants of the above indicated type.

The following are cited among the types of polymers constituting the pH independent membrane as an illustrative but not limited example: copolymers of
10 acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, neutral copolymers based on ethyl acrylate and methyl methacrylate and having an average molecular weight of 800,000 (Eudragit RS/RL/NE) ethylcellulose, polyethylene, polysiloxane, alone or
15 mixed with each other or with water-soluble pH independent polymers such as: hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, polyvinylpyrrolidone.

20 The granules coated with the membrane are dried, eg with hot air (about 50 degrees C) for about 30 minutes.

As previously mentioned the coating with the two membranes can also be done in the opposite order to that described.

25 The invention is illustrated by Examples 1 and 2. Example 3 is a reference Example.

Example 1

800g of mebeverine hydrochloride granulated with hydroxypropylmethylcellulose and with a particle size between 710 and 1300 μ was put in the UNI Glatt fluid bed container equipped with the Wurster insert.

- 5 This granulate was coated with a first membrane of Eudragit S, by spraying a suspension with the following composition with the atomiser: 468g of methylene chloride, 156g of isopropyl alcohol, 55.6g of Eudragit S, 5.5g of dibutyl phthalate and 28g of talc.
- 10 The coated granules were dried in hot air (about 50 degrees C) for 30 minutes and then the release was determined with the USP apparatus 2 (paddle), utilising the following sequence of artificial juices, 2 hours in 0.1N HCl, 1 hour in pH 6.2 buffer and the following
- 15 hours in pH 7.2 buffer.

The following results were obtained:

Time (hours)	1	2	3	4	5
Release (%)	8	14	16	70	97

- Then a second membrane of ethylcellulose was applied to 700g of these Eudragit S coated granules by spraying the following solution 199g of methylene chloride, 44g of ethyl alcohol, 4.3g of ethylcellulose, 8.6g of
- 20 hydroxypropylmethylcellulose and 1.5g of diacetylated monoglycerides and finally drying with air at 50 degrees C for about 30 minutes. The granules coated with the two membranes were analysed again as described above and the following results were obtained:

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Time (hours)	1	2	3	4	5	6	8
Release (%)	5	10	11	28	49	73	95

Example 2

700g of calcitonin granulated with lactose and hydroxypropylmethylcellulose as binder with a particle size between 710 and 1300 μ was put in the UNI Glatt container equipped with Wurster insert.

- 5 These granules were coated with a first membrane of ethylcellulose/hydroxypropylmethylcellulose, by spraying solution with the following composition with the atomiser: 200g of methylene chloride, 45g of ethyl alcohol, 6.4g of ethylcellulose, 6.4g of hydroxypropylmethylcellulose, and 1.4g of diacetylated monoglycerides.
- 10

- The coated granules were dried with hot air (about 50 degrees C) for 30 minutes and then its release was determined with the USP apparatus 2 (paddle), utilising the following sequence of artificial juices: 2 hours in HCl 0.1N, 1 hour in pH 6.2 buffer and the following hours in pH 7.2 buffer.
- 15

The following results were obtained:

Time (hours)	1	2	3	4	5
Release (%)	27	51	69	83	99

- Then a second Eudragit S membrane was applied to these coated granules, by spraying the following suspension:
- 20 134 g of methylene chloride, 65g of isopropyl alcohol, 23g of Eudragit S, 2.3g of dibutyl phthalate and 11.5g of talc and finally drying with air at 50 degrees C for about 30 minutes.

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The granules coated with the two membranes were analysed again as described above and the following results were obtained:

Time (hours)	1	2	3	4	5	6	8
Release ($\frac{1}{2}$)	2	3	7	26	58	72	98

Example 3

5 800g of mebeverine hydrochloride granulated with hydroxypropylmethylcellulose with a particle size between 710 and 1300 μ m was put in the UNI Glatt fluid bed container equipped with Wurster insert.

10 These granules were coated with ethylcellulose hydroxypropylmethylcellulose / Eudragit S membrane, by spraying a suspension with the following composition with an atomiser: 836g of methylene chloride, 418g of isopropyl alcohol, 5.8g of ethylcellulose, 11.8g of hydroxypropylmethylcellulose, 58.7g of Eudragit S, 3.7g of dibutyl phthalate and 29g of talc.

15 The coated granules were dried with hot air (about 45 degrees C) for 30 minutes and then the release was determined with the USP apparatus 2 (paddle) using the following sequence of artificial juices: 2 hours in 0.1 N HCl, 1 hour in pH 6.2 buffer and the following hours in pH 7.2 buffer.

The following results were obtained:

Time (hours)	1	2	3	4	5	6
Releases (%)	4	7	10	58	90	100

Example 4

Very small tablets of Ferritin, a protein that is destroyed by the gastric juices, were prepared. They had a diameter of 2.0 mm and a thickness of 2.2 mm, and the following composition:

Ferritin	80.0%
Magnesium Stearate	1.5%
Silicon dioxide	1.0%
Microcrystalline cellulose	13.5%
Hydrogenated castor oil	1.0%
Sodium Crosscarmellose	3.0%

- 5 2.2 kg of these Ferritin minitabets were put in the Versaglatt container (fluid bed coater) equipped with the Wurster insert.

They were coated first with a membrane of ethylcellulose aqueous dispersion (Aquacoat^R/FMC) and
10 hydroxypropyl methylcellulose, by spraying a suspension with the following composition:

-	Aquacoat ^R (30% aqueous dispersion w/w)	24.30 g
-	Methocel E% (10% aqueous solution w/w)	290.00 g
-	Dibutylsebacate	1.48 g
-	Talc	7.26 g

(total solid content of the suspension: 14% w/w)

- The coated minitabets were dried in hot air (about 60°C) for 30 minutes and then the release was determined with the USP apparatus 2 (paddle) in pH 6.8
15 buffer. The following results were obtained:

Time (minutes)	30	60	90
Release (%)	27	76	100

Then an aqueous acrylic resin dispersion (Eudragit L30D) was applied on these coated minitabets.

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It had the following composition:

-	Eudragit L30D (30% aqueous dispersion w/w)	273 g
-	Talc	33 g
-	Triethylcitrate	8 g
-	Deionized water	286 g

(total solid content: 20% w/w)

5 The double coated minitabets were dried with air at 50°C for about 30 minutes and analysed with the USP apparatus 2 (paddle) using the following sequence of artificial juices: 60' in 0.1 N HCl, 60' at pH 4.5 buffer and then at pH 6.8 buffer.

The following results were obtained:

Time (minutes)	60	120	150	180	210
Release (%)	2	10	38	85	100

10 This example illustrates a formulation targetting the small intestine where substantially all of the release occurs at pH 6.8 over a period of 1 to 1½ hours.

CLAIMS

1. A targeted drug release formulation for delivery of drugs to the small intestine and/or colon of a mammal consisting essentially of a plurality of multidose units each said unit having a particle size of less than about 5mm and consisting essentially of a core of a drug (free of aminosalicyclic acid functional groups and excluding anti-inflammatory and antiphlogistic drugs having a local action in the intestine, corticosteroids for the local treatment of chronic intestinal inflammation or irritation, and peppermint oil) surrounded by two membranes, one membrane consisting essentially of a pH dependent polymer which is substantially soluble at a pH greater than about 5.0, and the second of said membranes consisting essentially of one or more polymers such that said second membrane is substantially insoluble in but permeable to gastrointestinal fluids.

2. A targeted drug release formulation as claimed in Claim 1 wherein said formulation is characterised by the release of no more than about 10% drug into the stomach with substantially all of the remainder of the drug being released in the small intestine and/or colon in a period from about $\frac{1}{2}$ hour to about 8 hours.

3. A targeted drug formulation as claimed in Claim 1 wherein said formulation is characterised by the release of no more than about 10% of the drug at pH lower than 4.5 with substantially all of the remainder of the drug being released at a pH of 5.0 or greater in a period of from about $\frac{1}{2}$ hour to about 8 hours in simulated gastrointestinal media.

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4. The formulation of any one of Claims 1 to 3 in which the membrane containing the pH dependent polymer is interior to the other membrane.

5. The formulation of any one of Claims 1 to 3 in which the membrane containing the pH dependent polymer is exterior to the other membrane.

6. The formulation of any one of Claims 1 to 5 wherein the core of said multidose units comprises crystals, granules, pellets or minitables.

7. The formulation of any one of the preceding Claims wherein said pH dependent polymer is selected from anionic copolymers based on methacrylic acid and methacrylic acid methyl or ethyl ester, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate, shellac, hydroxypropylmethylcellulose acetate succinate, carboxymethylcellulose, cellulose acetate trimellitate, copolymers of maleic acid and derivatives of phthalic acid.

8. The formulation of any one of the preceding Claims where in said substantially insoluble membrane is selected from copolymers formed from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, neutral copolymers based on ethyl acrylate and methyl methacrylate and having an average molecular weight of 800,000, ethylcellulose, polyethylene, polysiloxanes and mixtures thereof.

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9. The formulation of Claim 8 further comprising a pH independent water soluble polymer selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, polyvinylpyrrolidone and mixtures thereof.

10. The formulation of any one of the preceding claims further comprising a plasticizer in at least one of the membranes.

11. The formulation of claim 8 wherein said substantially insoluble membrane is selected from ethyl cellulose and mixtures of ethylcellulose with hydroxypropylmethylcellulose in a ratio of about 1:5 to about 5:1.

12. A pharmaceutical dosage form comprising the formulation of anyone of the preceding claims further formulated in capsules, sachets, tablets or suspensions.

13. A pharmaceutical dosage form as claimed in any one of the preceding claim which is characterised by the release of no more than about 11% after 3 hours and no more than about 75% after 6 hours in simulated gastrointestinal juices.

14. A pharmaceutical dosage form as claimed in any one of Claims 1 - 12 which is characterised by the release of substantially all of the remaining drug in a period of about 1 to $1\frac{1}{2}$ hours at pH 6.8.

15. A method for preparing a targeted drug release formulation as defined in anyone of the preceding Claims comprising the steps of

A) preparing a plurality of drug containing cores said cores having a particle size no greater than about 5 mm,

B) coating said cores with two separate and distinctly characterised membrane layers wherein;

1) one said membrane layer consists essentially of a polymer which is soluble in gastrointestinal juices at a pH greater than about 5.0, and

2) wherein said second polymer layer consists essentially of a polymer which is substantially insoluble in gastrointestinal juices but permeable thereto;

C) if desired formulating said coated core into drug dose oral delivery forms selected from capsules, tablets, sachets and suspensions.

16. Method for the targeted and controlled release of drugs, said drug being as defined in Claim 1, in the intestine and particularly in the ileum and the colon, characterised in that the multidose form of the drug a membrane soluble at a given pH and an insoluble membrane which is permeable to intestinal fluids are applied consecutively, the order of application being unimportant.

17. Method according to Claim 16, characterised in that the drug is initially coated with a polymeric membrane, soluble in natural fluids (gastrointestinal juices) or artificial fluids (buffer solutions) over a certain pH, which is then in turn coated with another polymeric membrane which is insoluble but permeable to the above mentioned fluids.

18. Method according to Claim 17, characterised in that the drug is initially coated with a polymeric membrane, which is insoluble but permeable, which is then in turn coated with another polymeric membrane soluble above a certain pH in natural or artificial fluids.

19. Method according to Claim 18, characterised in that the drugs in multidose form consists of drugs in the form of crystals, granules, pellets or minitabets with a particle size comprised between 0.1 and 5.0 mm.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00688

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : A 61 K 9/24, A 61 K 9/54		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁵	A 61 K	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RÉLEVANT *		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP, A, 0239361 (KINAFORM TECHNOLOGY INC.) 30 September 1987 see the whole document ---	1-3,5-10,12-16,18-19
X	EP, A, 0148811 (LEJUS MEDICAL AKTIEBOLAG) 17 July 1985 see the whole document ---	1-3,5-10,12-16,18-19
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X	WO, A, 8503437 (A/S ALFRED BENZON) 15 August 1985 see the whole document ---	1,4-10,12,15-19
X	EP, A, 0277925 (LEJUS MEDICAL AKTIEBOLAG) 10 August 1988 see the whole document ---	1-3,5-16,18-19
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<p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
20th June 1991	6. 08. 91	
International Searching Authority	Signature of Authorised Officer:	
EUROPEAN PATENT OFFICE	J. Toribio	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ¹⁾ with indication, where appropriate, of the relevant passages	Relevant to Claim No
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A	GB, A, 2066070 (ROUSSEL-UCLAF) 8 July 1981 see the whole document & US, A, 4432966 cited in the application ---	1-19
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9100688
SA 46338

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/07/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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